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Health Effects Assessment for Acetonitrile

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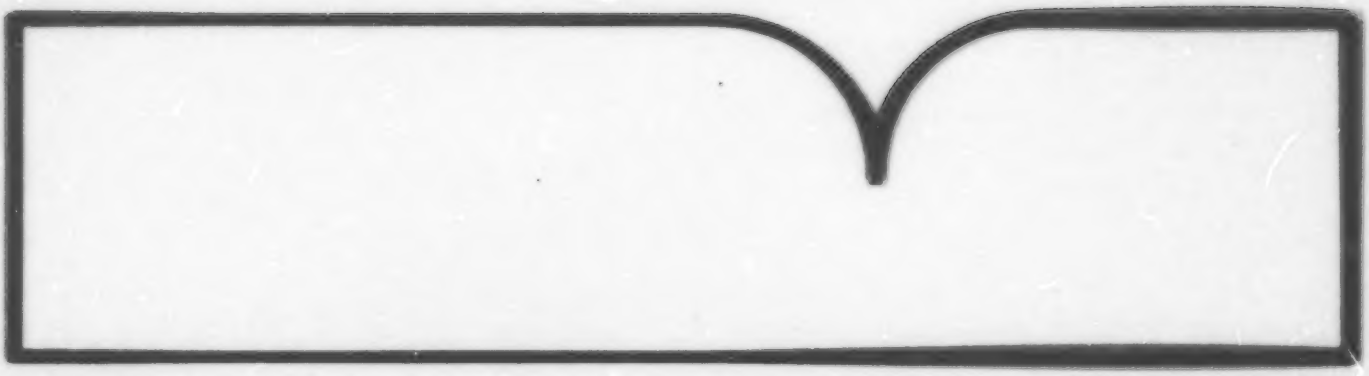

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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with acetonitrile. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary reflecting limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1983a. Reportable Quantity Document for Acetonitrile. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985a. Health and Environmental Effects Profile for Acetonitrile. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The RfD_{SO} (4.6 mg/day) and RfD_{O} (0.5 mg/day) values for acetonitrile were based on a mouse NOAEL of 39 mg/kg/day derived from a 92-day inhalation study (Coate, 1983a).

The RfD_{SI} (9.1 mg/day) and RfD_{I} (0.91 mg/day) values were derived from same study. The inhalation values are higher than the oral values because applications of an absorption factor is necessary in extrapolation from inhalation to oral exposure. A CS of 26 was based on teratogenicity and fetotoxicity in hamsters treated with a single oral dose of 200 mg/kg of acetonitrile on day 8 of gestation (Willhite, 1983).

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BUN	Blood urea nitrogen
bw	Body weight
CAS	Chemical abstract service
CS	Composite score
Ig	Immunoglobulin
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RBC	Red blood cell cholinesterase
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
STEL	Short-term exposure level
TLV	Threshold limit value
TSH	Thyroid stimulating hormone
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected physical and chemical properties and environmental fate of acetonitrile are listed in Table 1-1.

In the atmosphere, acetonitrile should exist primarily in the vapor phase and is expected to react with ozone and photochemically-generated hydroxyl radicals. The atmospheric half-life listed in Table 1-1 is based on the contribution from both ozone and hydroxyl radical reactions. It is based on an ozone reaction rate constant of $\leq 1.5 \times 10^{-19}$ cm³/molecule-sec, an ambient ozone concentration of 10^{12} molecule/cm³, a hydroxyl reaction rate constant of $\sim 5 \times 10^{-14}$ cm³/molecule-sec at 25°C and an ambient hydroxyl concentration of 8.0×10^{5} molecule/cm³. In moderately polluted air, the hydroxyl reaction rate is 10 times faster than in typical air, and a half-life of <20 days has been calculated. The complete water solubility of acetonitrile suggests that dissolution into clouds and rain droplets may occur, with subsequent removal by rainfall (U.S. EPA, 1985a). In water, microbial degradation and volatilization appear to be the significant fate and transport processes. At 20-25°C, the half-life in natural waters can be estimated to be ~1-2 weeks from biodegradation study data in river water and from volatility estimations (U.S. EPA, 1985a). Adsorption to suspended solids and sediments and bioaccumulation in aquatic organisms should not be significant. The half-life of acetonitrile in soil could not be located in the available literature. Laboratory data indicate that acetonitrile is susceptible to significant microbial degradation. Significant evaporation from soil surfaces may also occur. Estimated K_{oc} values ranging from 2-15 suggest that acetonitrile would be highly mobile and, therefore, would easily leach in soil (U.S. EPA, 1985a).

TABLE 1-1

Selected Physical and Chemical Properties and Half-Lives for Acetonitrile*

Property	Value
CAS number:	75-05-8
Chemical class:	alkyl nitrile
Molecular weight:	41.05
Vapor pressure at 20°C:	74 mm Hg
Water solubility:	completely miscible
Log octanol/water partition coefficient:	-0.34
Bioconcentration factor:	0.3 (estimated)
Soil adsorption coefficient:	2-15 (estimated)
Half-lives:	
Air	~42 days(estimated)
Water	~1-2 weeks
Soil	NA

*Source: U.S. EPA, 1985a

NA = Not available

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Quantitative data regarding the absorption of acetonitrile after oral exposure could not be located in the available literature. Several pharmacokinetic studies (Ahmed and Farooqui, 1982; Silver et al., 1982) and toxicity studies (Pozzani et al., 1959a; Willhite, 1983), however, imply that some acetonitrile is absorbed after ingestion. Ahmed and Farooqui (1982) identified cyanide in the liver, kidney and brain of rats after oral treatment with 2460 mg/kg of acetonitrile in saline. Silver et al. (1982) reported that 11.8% of the dose administered orally to rats was excreted as thiocyanate in the urine within 24 hours after ingestion. The toxicity studies, discussed in Chapter 3, resulted in adverse effects after oral exposure to acetonitrile.

2.2. INHALATION

Quantitative data regarding the absorption of acetonitrile in humans after inhalation exposure are available (Dalhamn et al., 1968a,b). In a group of 16 human subjects who were cigarette smokers, an average of 74% absorption of acetonitrile was measured when the smoke was held in the mouth for 2 seconds and was not inhaled. When the subjects were classified by the number of cigarettes smoked/day, a slight but statistically significant ($p<0.05$) inverse correlation was noted between the smoking rate and the extent of acetonitrile absorption (Dalhamn et al., 1968a). When the cigarette smoke was inhaled into the lungs, absorption of acetonitrile increased to 91% (Dalhamn et al., 1968b).

The only other quantitative study on absorption is that conducted by Pozzani et al. (1959a), in which three beagle dogs were exposed for 4 hours to acetonitrile vapor at an air concentration of 16,000 ppm (27,000 mg/m³). After ~1 hour, blood cyanide concentrations were 33-53 µg/100 mℓ blood. Blood cyanide levels peaked after ~3 hours (305-433 µg/100 mℓ blood) and were somewhat reduced at the end of the 4-hour exposure period (266-291 µg/100 mℓ blood). The authors did not discuss this pattern of absorption but noted one "analytical artifact" during the elimination phase of this study. Given the small number of animals used in this study and possible problems in the analytical technique, these data cannot be used to derive a rate coefficient for absorption. Nonetheless, the data indicate qualitatively that acetonitrile is absorbed rapidly upon inhalation and suggest that the dogs may have been nearing steady-state blood concentrations at 3-4 hours after exposure.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Pertinent data regarding the toxicity of acetonitrile after oral exposure could not be located in the available literature.

3.1.2. Inhalation. Pozzani et al. (1959a) investigated the toxicity of acetonitrile in subchronic inhalation experiments in rats, dogs and monkeys. Wistar rats (15/sex/exposure level plus two sets of controls of 15/sex) were exposed to 0, 166 ppm (279 mg/m³), 330 ppm (554 mg/m³) and 655 ppm (1100 mg/m³) acetonitrile 7 hours/day, 5 days/week for 90 days. At the 166 or 330 ppm levels, no statistically significant changes were observed in body weights, organ weights or histological appearance of selected major organs. At 655 ppm, 10/27 males and females had pulmonary lesions as evidenced by "alveolar capillary congestion and/or focal edema, often accompanied by bronchial inflammation, desquamation and hypersecretion of mucus." Central cloudy swelling of the liver and tubular cloudy swelling of the kidney were observed in 7/27 and 8/27 rats, respectively. These results were statistically significant ($p<0.05$) relative to controls. Although no lesions were found in the adrenals, pancreas, spleen, testes and trachea, 1/5 brains examined in the 655 ppm exposure group had focal cerebral hemorrhage, an effect similar to that reported in monkeys at $\leq$655 ppm acetonitrile.

As a preliminary inhalation experiment, Pozzani et al. (1959a) exposed one or two rhesus monkeys/exposure levels to 330 ppm (554 mg/m³), 660 ppm (1110 mg/m³) and 2510 ppm (4210 mg/m³) acetonitrile for 7 hours/day for up to 99 days. No air-exposed controls were maintained. The monkey exposed to 2510 ppm died with severe pulmonary effects after the second day of exposure, and two monkeys exposed to 660 ppm died after 23 and 51 days.

Brain hemorrhages, adverse changes in the lung (e.g., atelectasis and pneumonitis) and cloudy swelling of the renal convoluted tubules were reported in the monkeys exposed to acetonitrile at 660 ppm for >2 days. The monkey exposed to 330 ppm survived until sacrifice at 99-days, but had chronic pneumonitis as evidenced by diffuse proliferation of alveolar septa, monocytic infiltration and pleural adhesions. Pozzani et al. (1959a) also exposed three adult male mixed breed dogs and three adult male rhesus monkeys to 350 ppm (588 mg/m³) acetonitrile, 7 hours/day, 5 days/week for 91 days. Both the monkeys and dogs had pulmonary abnormalities. The dogs exhibited a transient depression in hematocrit and hemoglobin values but no significant deviation in erythrocyte counts. Brain hemorrhages were observed in all three monkeys and cloudy swelling of the convoluted kidney tubules was noted in two of the three exposed monkeys. The monkeys also exhibited excitability and over-extension reflexes.

Groups of 10 male and 10 female Fischer 344 rats and 10 male and 10 female B6C3F1 mice were exposed to 0, 25, 50, 100, 200 or 400 ppm (0, 42, 84, 168, 336 or 672 mg/m³) of acetonitrile vapor 6 hours/day, for 65 days during a 92-day experimental period (Coate, 1983a,b). Parameters evaluated included body and organ weight, clinical chemistry, hematology, immune functions after 10 days of exposure (mice), sperm count, motility and morphology, vaginal cytology, levels of serum, T_3 or TSH or both, urinary cyanide levels and the histology of the major organs from the control group and the 400 ppm exposure group, the liver from the 100 and 200 ppm exposure groups and the nasal turbinates from all exposure groups. The only statistically significant effects observed in rats were decreased mean leucocyte counts in males exposed to $\geq$100 ppm of acetonitrile and females exposed to 400 ppm of acetonitrile. Body weights were slightly increased during the

study in females exposed to ≥100 ppm and males exposed to 400 ppm, but there were no statistically significant differences in terminal body weights between test and control rats. The biological significance of the decreased leucocyte counts is unclear. Males exposed to 400 ppm of acetonitrile had slightly increased heart-to-body weight ratios, but no cardiac histopathological alterations. Hepatocyte vacuolization was observed in all groups evaluated including controls, but the intensity of the vacuolization was slightly greater in the female rats exposed to 400 ppm of acetonitrile. No other histopathological alterations were reported.

The statistically significant effects in the mice included decreased BUN levels, RBC counts and hematocrits in females exposed to 200 or 400 ppm of acetonitrile. Hepatic vacuolization and hypertrophy were observed at all dose levels evaluated including controls, but the intensity of the hepatic lesions appeared greater in male and female mice exposed to 200 or 400 ppm of acetonitrile. Elevated relative liver weights were observed in males at 400 ppm and in females at 100 and 200 ppm. A dose-related decrease in leucocyte count and serum IgG levels occurred, but did not appear to indicate specific T- or B-lymphocyte dysfunction, and the biological significance of these findings is unclear.

Immuquest Labs, Inc. (1984) exposed groups of unspecified numbers of female B6C3F1 mice to acetonitrile at 0, 100, 200 or 400 ppm (0, 168, 336 or 672 mg/m³) 6 hours/day, 5 days/week for 90 days. There were no effects on physical appearance, body weights or gross appearance at necropsy. Mice in the 200 and 400 ppm groups had atrophy of the thymus, which was noted upon histopathological examination. Slight vacuolization of hepatocytes accompanied by hydropic degeneration was also observed at 400 ppm. There were no treatment-related effects on selected clinical chemistries, but mice at 200

and 400 ppm had dose-related decreases in hematocrits, blood hemoglobin concentration, and erythrocyte and leucocyte counts. Changes in hematological parameters were not significant at 100 ppm. No significant effects on organ weights were observed, but the investigators noted a trend toward depressed thymus weights at 200 and 400 ppm.

After 14 days, Immuquest Labs, Inc. (1984) evaluated immune function in mice exposed by the same protocol. A significant dose-related depression of serum concentration of IgG was observed in all exposed mice, but no effects were observed on the Cunningham plaque-forming response to sheep erythrocytes, the lymphocyte blastogenesis test, delayed hypersensitivity response or susceptibility to challenge with PYB6 tumor cells.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding the systemic toxicity of acetonitrile after chronic oral exposure could not be located in the available literature.

3.2.2. Inhalation. Pertinent data regarding the systemic toxicity of acetonitrile after chronic inhalation exposure could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Willhite (1983) studied the teratogenicity of acetonitrile in groups of 6-12 female Syrian Golden hamsters. The hamsters were exposed to acetonitrile in distilled water by oral intubation on day 8 of gestation (the early primitive streak stage of embryogenesis) at levels of 100, 200, 300 and 400 mg/kg. Controls were treated with distilled water. At the 400 mg/kg dose level, signs of maternal toxicity were evident after 2.5 hours. There was a statistically significant ($p<0.05$) increase in the incidence of malformed offspring at the 300 and 400 mg/kg doses. These malformations

included exencephaly, encephalocele and rib abnormalities. In addition, 2/5 litters produced by dams treated with 100 mg/kg of acetonitrile had single pups with an encephalocele; however, this was apparently not significantly different from control incidence. At 200 or 400 mg/kg, there was a statistically significant ($p<0.05$) increase in fetal resorptions. At all dose levels, a statistically significant decrease ($p<0.05$) in average fetal body weight was found.

In a range-finding teratogenicity study by IRDC (1980), groups of five mated Charles River COBS CD rats were treated with acetonitrile in distilled water by gavage at 0, 200, 375, 750, 1500 or 3000 mg/kg/day on days 6-19 of gestation. Day 0 of gestation was defined as the day in which evidence of mating, a sperm positive vaginal smear or the presence of a copulatory plug, was observed. Dams were sacrificed on gestation day 20. Parameters of toxicity evaluated included mortality, appearance, behavior and body weights of dams, the numbers and location of viable fetuses, early and late resorptions, corpora lutea and total implantation. Gross appearance at necropsy was recorded at sacrifice and at time of death for those that did not survive to termination. Treatment-related mortality occurred in three dams receiving 375 mg/kg/day and in all dams at $\geq$750 mg/kg/day. Rats in these groups also had staining of haircoats, abnormal ocular and nasal discharge and marked, dose-related mean body weight losses. No adverse maternal effects were observed at 200 mg/kg/day. Meaningful pregnancy data were obtained only for the 200 and 375 mg/kg/day groups because of mortality at higher doses. No adverse effects were observed at 200 mg/kg/day. A marked increase in early resorptions was observed in both dams surviving at 375 mg/kg/day, compared with controls.

In the definitive teratogenicity study performed by IRDC (1981), groups of 25 Charles River COBS rats were treated by gavage with 0, 125, 190 and 275 mg/kg/day of acetonitrile in water on days 6-19 of gestation (day 0 = day on which there was evidence of mating). On day 20 of gestation, the dams were sacrificed. At the 275 mg/kg/day dose level, two dams died, while there was reduced body weight gain and emaciation in two others. Increases in the mean number of early resorptions and postimplantation losses, and a decrease in the mean number of viable fetuses were also observed at the 275 mg/kg/day treatment level. These effects were not statistically significant when compared with concurrent controls, but were significant when compared with historic controls. At the 125 or 190 mg/kg/day dose levels, these differences were not observed. There was no increased incidence of fetal anomalies, but there was a slight increase in the incidence of unossified sternebrae in all treated groups as compared with concurrent but not historic controls.

Pregnant rabbits appear to be more sensitive than rats to the toxicity of acetonitrile. Argus Research Laboratories, Inc. (1984) administered acetonitrile in deionized water by gavage to groups of 25 artificially inseminated rabbits on days 6-18 of gestation at 0, 2.0, 15.0 or 30.0 mg/kg/day. Dams were sacrificed on gestation day 29. Five maternal deaths and two abortions attributed to acetonitrile occurred at 30.0 mg/kg/day. These effects were not observed at lower doses. High-dose dams had a significant ($p<0.01$) decrease in body weight, accompanied by anorexia during the treatment period that was followed by a rebound phenomenon during the posttreatment period so that terminal body weights were higher than controls on gestation days 19-24. Although body weights at 15.0 mg/kg/day were not significantly depressed during the treatment period, this group also

exhibited the rebound phenomenon. A significant (p=0.011) decrease in the average number of live fetuses/litter was observed at 30.0 mg/kg/day, accompanied by a slight but not significant increase in the incidence of resorptions. There were no treatment-related effects on the incidence of pregnancy, number of corpora lutea, implantations, fetal body weight or sex ratio. No treatment-related fetal malformations were observed, but an increase in the incidence of an extra ossification site in the parietal bones was observed in four fetuses in two high dose litters (p=0.015), which was not significant when expressed in terms of incidences among litters.

3.3.2. Inhalation. Willhite (1983) exposed groups of 6-12 Syrian golden hamsters to acetonitrile at 0, 1800, 3800, 5000 or 8000 ppm (0, 3022, 6380, 8395 or 13,431 mg/m³) for 60 minutes on day 8 of gestation. Inhalation of 1800 ppm did not induce fetal malformations or signs of toxicity in the dams. One dam exposed to 3800 ppm showed dyspnea, tremors, hypersalivation, ataxia and hypothermia after 60 minutes of exposure, and died 3 hours later. The other five hamsters showed no signs of intoxication at this exposure level and their offspring were normal. At 5000 ppm, all animals were irritated and salivated excessively. One hamster had dyspnea, hypothermia and tremors after 60 minutes exposure, and died 5 hours later. Six abnormal fetuses were found in two litters taken from other hamsters exposed at this level. Malformations seen were exencephaly, encephalocele and rib fusions. Four hamsters exposed for 60 minutes to 8000 ppm (13,431 mg/m³) showed signs of acute toxicity and three died 1.5 hours after termination of exposure. Histopathological studies failed to reveal any changes in liver, kidney and lungs. Offspring of these dams were afflicted with severe axial skeletal disorders in five of the nine surviving litters. Average fetal body weights were also decreased when compared with litters from dams

exposed only to chamber air. One fetus showed extrathoracic ectopia cordis with accompanying defects in the sternum (a rare syndrome). A significant increase was seen in the number of abnormal fetuses at the 5000 (8395 mg/m³) or 8000 (13,431 mg/m³) ppm level when compared with control animals exposed to chamber air. In addition, there was a significant increase in the number of malformed offspring at 5000 ppm (8395 mg/m³) when compared with the lower level of exposure [3800 ppm (6379 mg/m³)], which was also true when 8000 (13,431 mg/m³) and 5000 (8395 mg/m³) ppm levels were compared.

No adverse effects were observed in sperm motility and morphology or in vaginal cytology of F344 rats or B6C3F1 mice exposed to ≤400 ppm of acetonitrile, 6 hours/day, 5 days/week for 13 weeks (Coate, 1983a,b) (see Section 3.1.2.).

3.4. TOXICANT INTERACTIONS

In a study designed to assess toxicant interactions based on the assumption of dose additivity, Pozzani et al. (1959b) determined the oral LD_{50}s and inhalation LC_{50}s of binary mixtures of acetonitrile with acetone, carbon tetrachloride, toluene, propylene oxide or epichlorohydrin. Greater than additive potency was noted with mixtures of acetonitrile and acetone for both oral (3.6 times greater) and inhalation (2.7 times greater) toxicity. In a similar study, Smyth et al. (1969) reported greater than additive potency for mixtures of acetonitrile with either acetone (3.6 times greater) or dioxane (3.2 times greater) based on determinations of oral LD_{50}s.

Carbon tetrachloride pretreatment may reduce the acute toxic potency of acetonitrile. After carbon tetrachloride pretreatment, mice that were subsequently exposed to 5000 ppm (8395 mg/m³) acetonitrile by inhalation for 1 hour or 575 mg/kg by the intraperitoneal route showed sharply reduced

fatalities (Willhite, 1981; Willhite and Smith, 1981). Without carbon tetrachloride pretreatment, deaths from inhalation exposure were 10/10; with pretreatment, deaths were reduced to 2/10. With the injection dose, after pretreatment, deaths were 0/10; without carbon tetrachloride pretreatment, deaths were 7/10. Sodium thiosulfate was also protective, and sodium nitrite was less protective (Willhite, 1981). Tanii and Hashimoto (1984) found that an oral dose of 9.96 mmol/kg bw of acetonitrile (in water) killed 8/10 mice pretreated with olive oil, whereas 0/10 mice pretreated with carbon tetrachloride died. Arbuzov (1975) reported that acetonitrile-induced lung edema was prevented by compounds that blocked N-cholino-receptors or by glucocorticoids or SH group donors, but sodium nitrite and sodium thiosulfate did not prevent edema.

Tanii and Hashimoto (1986) reported that ethanol treatment enhanced the acute toxicity of acetonitrile in vivo when administered orally to mice.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenicity of acetonitrile in humans after oral exposure could not be located in the available literature.

4.1.2. Inhalation. Pertinent data regarding the carcinogenicity of acetonitrile in humans after inhalation exposure could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. Pertinent data regarding the carcinogenicity of ingested acetonitrile could not be located in the available literature.

4.2.2. Inhalation. A preliminary subchronic inhalation study for acetonitrile is in progress using rats and mice (NTP, 1986).

4.3. OTHER RELEVANT DATA

Florin et al. (1980) tested acetonitrile on four strains of Salmonella typhimurium and noted no mutagenic activity. U.S. EPA (1982) reported that the National Toxicology Program is conducting additional mutagenicity tests on acetonitrile. Published reports of these studies could not be located in the literature.

Brown and Donelly (1984) reported mutagenic activity in acidic, basic and neutral extracts from a waste stream of a petrochemical plant where acetonitrile was being purified. The waste stream contained 3.46% acetonitrile, 0.92% acetamide, 0.09% "R-OH" and 0.5% "heavy ends." The chemical composition of the latter two fractions were not identified.

Acetonitrile has been found to be unacceptable as a solvent for use in mutagenicity assays (Arimoto et al., 1982; Kawalek and Andrews, 1980; Maron et al., 1981).

4.4. WEIGHT OF EVIDENCE

According to U.S. EPA (1986) guidelines, acetonitrile should be placed in Group D, which indicates that there are insufficient data to allow any conclusion regarding the carcinogenicity of acetonitrile. IARC has not classified acetonitrile, but an IARC classification of 3, cannot be classified, seems most appropriate.

5. REGULATORY STANDARDS AND CRITERIA

NIOSH (1978) recommended a TWA-TLV of 20 ppm (34 mg/m³) for acetonitrile, while OSHA (1985) listed an acceptable occupational exposure level of 40 ppm (70 mg/m³) for acetonitrile.

The ACGIH (1985, 1986) has recommended a TLV of 40 ppm (70 mg/m³), with a STEL of 60 ppm (105 mg/m³) for acetonitrile to protect against organic cyanide poisoning and injury to the respiratory system based on the human studies of Pozzani et al. (1959b) and by analogy to the more toxic chemical, acrylonitrile. Acetonitrile is designated by the skin notation indicating the potential contribution of dermal absorption.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). Data regarding subchronic oral toxicity of acetonitrile could not be located in the available literature. In Section 6.2.1., an RfD_O of 6.5×10^{-3} mg/kg/day or 0.45 mg/day for a 70 kg human was derived by applying an uncertainty factor of 1000 and a modifying factor of 3 to a NOAEL of 19.3 mg/kg/day resulting from inhalation exposure of mice to 100 ppm (168 mg/m³), 6 hours/day, 5 days/week (Coate, 1983b).

An RfD_{SO} of 6.5×10^{-2} mg/kg/day (4.6 mg/day) can be derived by dividing the NOAEL of 19.3 mg/kg/day by a modifying factor of 3 and an uncertainty factor of 100 rather than 1000.

6.1.2. Inhalation (RfD_{SI}). Subchronic inhalation experiments with acetonitrile include a 90-day experiment in rats, dogs and monkeys (Pozzani et al., 1959a), a 92-day study using rats (Coate, 1983a) and mice (Coate, 1983b) and a 90-day study using mice (Immuquest Labs, Inc., 1984). Pozzani et al. (1959a) determined NOAELs using rats at 166 and 330 ppm (279 and 554 mg/m³) 7 hours/day, 5 days/week. At 330 ppm for 7 hours/day, monkeys developed lesions of chronic pneumonitis and at 350 ppm (588 mg/m³), 7 hours/day for 91 days, dogs developed pulmonary irregularities and monkeys developed brain hemorrhages and lung and kidney lesions. The investigators concluded that monkeys were more sensitive than rats to the toxic effects of acetonitrile. Coate (1983a) observed elevated relative heart weight in male rats and increased intensity of hepatocellular hypertrophy in female rats at 400 ppm (672 mg/m³), 6 hours/day on 65/92 days. No adverse effects were observed at 200 ppm (336 mg/m³). In mice, however, 200 ppm was associated with decreased erythrocyte counts and hematocrits in females and increased intensity of hepatocytic vacuolization and hypertrophy (Coate, 1983b). No

adverse effects in mice were noted at 100 ppm (168 mg/m³). The 90-day inhalation study by Immuquest Labs, Inc. (1984) confirms that 100 ppm is a NOAEL in mice.

Mice appear to be more sensitive than rats to the effects of acetonitrile. Although monkeys and dogs may be more sensitive than mice, these species were only examined in preliminary evaluations utilizing few animals at a single exposure level. In addition, rabbits were shown to be more sensitive than rodents in teratology evaluations. Considering all of the evidence, the most appropriate basis for an RfD_{SI} is the mouse NOAEL of 39 mg/kg/day (Coate, 1983b). The mg/kg/day dose was calculated as follows: 168 mg/m³ x 0.039 m³/24 hours (mouse ventilatory volume, U.S. EPA, 1980) x 6 hours/24 hours x 5 days/7 days ÷ 0.03 kg.

In developing an RfD_{SI}, a modifying factor of 3 is applied to account for the data that suggests that the mouse may not be the most sensitive species. In addition, an uncertainty factor of 100 is applied to account for interspecies and interindividual variability resulting in an RfD_{SI} of 0.13 mg/kg/ day or 9.1 mg/day for a 70 kg human.

6.2. REFERNCE DOSE (RfD)

6.2.1. Oral (RfD_0). No oral data appropriate for RfD estimation were located. In the absence of oral data, inhalation data may be utilized. This was the approach taken in U.S. EPA (1985a); however, U.S. EPA (1985a) did not have access to the studies of Coate (1983a,b) nor that of Argus Research Laboratories, Inc. (1984). These data indicate that rats are not only apparently less sensitive to acetonitrile than monkeys or dogs, but also appear to be less sensitive than mice or rabbits. The available inhalation studies are reviewed in Section 6.1.2. As described in that section, the mouse inhalation NOAEL of 39 mg/kg/day is chosen as the most appropriate basis to estimate an RfD_0. An absorption efficiency of 50% is

utilized to estimate an oral NOAEL resulting in an equivalent oral estimate of 19.5 mg/kg/day. Applying a modifying factor of 3 to account for concerns that adequate toxicity evaluations have not been conducted in what appear to be the most sensitive species, and an uncertainty factor of 1000 (10 to estimate an RfD_0 from subchronic data, 10 for interspecies variability and 10 for intraspecies variability) results in an RfD_0 estimate of 6.5×10^{-3} mg/kg/day or 0.46 mg/day for a 70 kg human.

The only oral experiments that provided data suitable for calculation of CSs were the developmental toxicity studies using hamsters (Willhite, 1983), rats (IRDC, 1981) and rabbits (Argus Laboratories, Inc., 1984). Willhite (1983) noted a significant increase in malformations in hamsters given a single oral dose of 200 mg/kg on day 8 of gestation and IRDC (1981) noted maternotoxic and fetotoxic effects in rats treated orally with 275 mg/kg/day during organogenesis. CSs for these effects are calculated and presented in Table 6-1. These CSs differ somewhat from those calculated by U.S. EPA (1985a) primarily because of differences in reference body weights for hamsters; however, the study of Willhite (1983) still yields the highest CS.

6.2.2. Inhalation (RfD_I). Chronic inhalation toxicity data were not available for acetonitrile. The most appropriate RfD_I is derived, therefore, by applying an uncertainty factor of 10 to the RfD_{SI} of 0.13 mg/kg/day (9.1 mg/day) based on the NOAEL of 39 mg estimated for mice exposed to 100 ppm (168 mg/m^3) in the subchronic study by Coate (1983b). The resulting RfD_I is 1.3×10^{-2} mg/kg/day or 0.91 mg/day for a 70 kg human.

The effects of subchronic inhalation exposure of rats, dogs, monkeys and mice (Pozzani et al., 1959a; Coate, 1983a,b), as well as the teratogenic and fetotoxic effects in hamsters of inhaling acetonitrile during gestation

(Willhite, 1983;), are suitable for calculation of inhalation CSs. The data used to calculate MEDs and CSs are presented in Table 6-1. The values for the MEDs differ somewhat from those reported by U.S. EPA (1985a) primarily because the default values currently recommended by the U.S. EPA (1985b) differ from the values used in the preparation of the previous document; however, the highest CS is still associated with an oral, not an inhalation, study.

6.3. CARCINOGENIC POTENCY (q_1^*)

Data are not sufficient for estimation of the carcinogenic potential of acetonitrile after oral or inhalation exposure.

TABLE 6-1

Composite Scores for the Toxicity of Acetonitrile by Oral/Inhalation Exposure

Route	Species/Strain	Sex	Exposure Dosage	Human MED[a] (mg/day)	RV_d	Effect	RV_e	CS	Reference
Inhalation	rat/Carworth Farms-Wistar	M/F	1100 mg/m³, 7 hours/day, 5 days/week for 90 days (146 mg/kg/day)[b]	175[c]	2.1	Reversible pulmonary inflammation; renal hepatic cloudy swelling (possibly focal cerebral hemmorhage)	5	10.5	Pozzani et al.,1959a
Inhalation	dogs/hybrid	M	588 mg/m³, 7 hours/day, 5 days/week for 90 days (41.5 mg/kg/day)[d]	164.4[c]	2.2	Focal emphysema and proliferation of lung septa, transient depression of hematocrit and hemoglobin levels	8	17.6	Pozzani et al.,1959a
Inhalation	monkey/rhesus	M	554 mg/m³, 7 hours/day, 5 days/week for 90 days (77.9 mg/kg/day)[e]	264.6[c]	1.9	Excitability; overextension reflexes; focal dural and subdural hemorrhage; pneumonitis	8	15.2	Pozzani et al., 1959a
Inhalation	mice/B6C3F1	M/F	336 mg/m³, 6 hours/day, 5 days/week for 99 days (77.9 mg/kg/day)[e]	41.2[c]	3.1	Increased intensity of hepatic vacuolization and hypertrophy without change in organ weight	3	9.3	Coate, 1983b
Inhalation	hamster/Syrian golden	F	6380 mg/m³, 1 hour on day 8 of gestation (246.8 mg/kg/day)[g]	217.7[c]	2.0	Teratogenic effects including exencephaly, encephalocele and rib fusions	10	20	Willhite, 1983
Oral	hamster/Syrian golden	F	200 mg/kg on day 8 of gestation	176.4[c]	2.7	Significant teratogenic effects	10	21	Willhite, 1983
Oral	rats/Charles River COBS	F	275 mg/kg/day on days 6-19 of gestation	3291.7	1	Fetotoxic effects, maternal mortality, reduced maternal weight	8	8	IRDC, 1981
Oral	rabbit	F	30 mg/kg/day on days 6-18 gestation	795	1.2	Fetotoxic effects	8	9.2	Argus Research Labs, Inc., 1984

[a]The MED is obtained by multiplying the exposure dose in mg/kg/day by the cube root of the animal to human body weight ratio and by the reference human body weight (70 kg).
[b]Based on the rat inhalation rate of 0.223 m³/day and reference body weight of 0.35 kg (U.S. EPA, 1985b).
[c]An uncertainty factor of 10 was applied to expand from subchronic to chronic exposure.
[d]Based on the dog inhalation rate of 4.3 m³/day and reference body weight of 12.7 kg (U.S. EPA, 1985b).
[e]Based on the monkey inhalation rate of 5.4 m³/day and reference body weight of 8.0 kg (U.S. EPA, 1985b).
[f]Based on the mouse inhalation rate of 0.039 m³/day and reference body weight of 0.03 kg (U.S. EPA, 1985b).
[g]Based on the hamster inhalation rate of 0.13 m³/day and reference body weight of 0.14 kg (U.S. EPA, 1985b).

7. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1986. Cincinnati, OH. p. 9.

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values, 5th ed. Cincinnati, OH. p. 8-9.

Ahmed, A.E. and M.Y.H. Farooqui. 1982. Comparative toxicities of aliphatic nitriles. Toxicol. Lett. 12(2-3): 157-163.

Arbuzov, E.E. 1975. Pathogenesis of toxic lung edema in rats caused by acetonitrile. Farmakol. Toksikol. Nov. Prod. Khim. Sint., Mater. Resp. Konf., 3rd Meeting Date 1974. p. 155-156. (CA 86:134455m)

Argus Research Laboratories, Inc. 1984. Embryofetal toxicity and teratogenicity study of acetonitrile in New Zealand white rabbits (Segment II evaluation). Office of Toxic Substances submission. Microfiche No. OTS 507279.

Arimoto, S., N. Nakano, Y. Ohara, K. Tanaka and H. Hayatsu. 1982. A solvent effect on the mutagenicity of tryptophan-pyrolyzate mutagens in the Salmonella/mammalian microsome assay. Mutat. Res. 102(20): 105-112.

Brown, K.W. and K.C. Donnelly. 1984. Mutagenic activity of the liquid waste from the production of acetonitrile. Bull. Environ. Contam. Toxicol. 32(6): 742-748.

Coate, W.B. 1983a. 90-Day subchronic toxicity study of acetonitrile in Fischer 344 rats. Final Report (revised). Submitted to National Toxicology Program by Hazleton Laboratories America, Inc.

Coate, W.B. 1983b. 90-Day subchronic toxicity study of acetonitrile in B6C3F1 mice. Final Report (revised). Submitted to National Toxicology Program by Hazleton Laboratories America, Inc.

Dalhamn, T., M.L. Edfors and R. Rylander. 1968a. Mouth adsorption of various compounds in cigarette smoke. Arch. Environ. Health. 16(6): 831-835.

Dalhamn, T., M.L. Edfors and R. Rylander. 1968b. Retention of cigarette smoke components in human beings. Arch. Environ. Health. 17: 746-748.

Florin, I., L. Futberg, M. Curvall and C.R. Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology. 15(3): 219-232.

Immuquest Labs, Inc. 1984. Limited toxicity of inhaled acetonitrile on the immune system of mice. OTS FYI submission. Microfiche No. FYI-AX-0284-0292.

IRDC (International Research and Development Corporation). 1980. Pilot teratology study in rats. OTS 8(d) submission. Microfiche No. OTS 206221.

IRDC (International Research and Development Corporation). 1981. Acetonitrile (IR-79-162). Teratology study in rats. Unpublished study sponsored by Monsanto Company.

Kawalek, J.C. and A.W. Andrews. 1980. The effect of solvents on drug metabolism in vitro. Drug Metab. Dispos. 8(6): 380-384.

Maron, D., J. Katzenellenbogen and N. Bruce. 1981. Compatibility of organic solvents with the Salmonella/microsome test. Mutat. Res. 88(4): 343-350.

NIOSH (National Institute for Occupational Safety and Health). 1978. Criteria for a Recommended Standard...Occupational Exposure to Nitriles. U.S. DHEW, PHS, CDC, Cincinnati, OH. Publ. No. 78-212.

NTP (National Toxicology Program). 1986. Management Status Report. June, 1986.

OSHA (Occupational Safety and Health Administration). 1985. Permissible Exposure Limits. Code of Federal Regulations. 29 CFR 1910.1000.

Pozzani, U.C., C.P. Carpenter, P.E. Palm, C.S. Weil and J.H. Noir, III. 1959a. An investigation of the mammalian toxicity of acetonitrile. J. Occup. Med. 1: 634-642.

Pozzani, U.C., C.S. Weil and C.P. Carpenter. 1959b. The toxicological basis of threshold limit values: 5. The experimental inhalation of vapor mixtures by rats with notes upon the relationship between single dose inhalation and single dose and data. Ind. Hyg. J. p. 364.

Silver, E.H., S.H. Kuttab, T. Hasan and M. Hassan. 1982. Structural considerations in the metabolism of nitriles to cyanide *in vivo*. Drug Metab. Dispos. 10(5): 495-498.

Smyth, H.F., Jr., C.S. Weil, J.S. West and C.P. Carpenter. 1969. Exploration of joint toxic action: Twenty-seven industrial chemicals intubated in rats in all possible pairs. Toxicol. Appl. Pharmacol. 14(2): 340-347.

Tanii, H. and K. Hashimoto. 1984. Studies on the mechanism of acute toxicity of nitriles in mice. Arch. Toxicol. 55(1): 47-54.

Tanii, H. and K. Hashimoto. 1986. Influence of ethanol on the *in vivo* and *in vitro* metabolism of nitriles in mice. Arch. Toxicol. 58(3): 171-176.

U.S. EPA. 1980. Guidelines and Methodology for the Preparation of Health Effect Assessment Chapters of the Ambient Water Quality Criteria Documents. Federal Register. 45(231): 49347-49357.

U.S. EPA. 1982. Acetonitrile; Response to the Interagency Testing Committee. Federal Register. 47: 58020-58023.

U.S. EPA. 1983a. Reportable Quantity Document for Acetonitrile. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1983b. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985a. Health and Environmental Effects Profile for Acetonitrile. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985b. Reference Values for Risk Assessment. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1986. Guidelines for Carcinogen Risk Assessment. Federal Register. 51(185): 33992-34003.

Willhite, C.C. 1981. Inhalation toxicology of acute exposure to aliphatic nitriles. Clin. Toxicol. 18(8): 991-1003.

Willhite, C.C. 1983. Development toxicology of acetonitrile in the Syrian golden hamster. Teratology. 27(30: 313-325.

Willhite, C.C. and R.P. Smith. 1981. The role of cyanide liberation in the acute toxicity of aliphatic nitriles. Toxicol. Appl. Pharmacol. 59(3): 589-602.

APPENDIX

Summary Table for Acetonitrile*

	Species	Experimental Exposure/Dose	Effect	Reference Dose (RfD or RfD_S)	Reference
Inhalation					
RfD_{SI} (formerly AIS)	mouse	100 ppm (168 mg/m³), 6 hours/day, 65/92 days (39.0 mg/kg/day)	elevated relative liver weight, females	9.1 mg/day	Coate, 1983b
RfD_I (formerly AIC)	mouse	100 ppm (168 mg/m³), 6 hours/day, 65/92 days (39.0 mg/kg/day)	elevated relative liver weight, females	0.91 mg/day	Pozzani et al., 1959a
Oral					
RfD_{SO}	mouse	100 ppm (168 mg/m³), 6 hours/day, 65/92 days (19.3 mg/kg/day)	elevated relative liver weight, females	4.6 mg/day	Coate, 1983b
RfD_O	mouse	100 ppm (168 mg/m³), 6 hours/day, 65/92 days (19.3 mg/kg/day)	elevated relative liver weight, females	0.46 mg/day	Coate, 1983b
Maximum CS	hamster	200 mg/kg on day 8 of gestation, RV_d = 2.1	malformations RV_e = 10	CS = 21	Willhite, 1981

*An absorption factor of 0.5 was used for extrapolation from inhalation to oral exposure.